

We claim:

1. A penetrating peptide comprising at least one amino acid sequence selected from the group consisting of:
 - a) $(BX)_4Z(BX)_2ZXB$;
 - b) $ZBXB_2XBXB_2XBX_3BXB_2X_2B_2$;
 - c) $ZBZX_2B_4XB_3ZXB_4Z_2B_2$;
 - d) $ZB_9XBX_2B_2ZBXZBX_2$;
 - e) $BZB_8XB_9X_2ZXB$;
 - f) $B_2ZXZB_5XB_2XB_2X_2BZXB_2$;
 - g) $XB_9XBXB_6X_3B$;
 - h) $X_2B_3XB_4ZBXB_4XB_nXB$;
 - i) $XB_2XZBXZB_2ZB_3X_3BZXB_3B$;
 - j) $BZXBXZX_2B_4XBX_2B_2XB_4X_2$;
 - k) $BZXBXZX_2B_4XBX_2B_2XB_4$;
 - l) $B_2XZ_2XB_4XBX_2B_5X_2B_2$;
 - m) $B_qX_tZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
 - n) $B_2ZX_3ZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
 - o) $X_3ZB_6XBX_3BZB_2X_2B_2$; and
 - p) at least 12 contiguous amino acids of any of peptides a) through o)

wherein

q is 0 or 1;

m is 1 or 2;

n is 2 or 3;

t is 1 or 2 or 3; and

X is any amino acid;

B is a hydrophobic amino acid; and

Z is a charged amino acid;

wherein said penetrating peptide is capable of translocating across a biological barrier.

2. The penetrating peptide of claim 1, wherein the amino acid sequence is selected from the group consisting of:
 - a) SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 24, 25, 26, 27, 28 and 29;
 - b) a variant of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 24, 25, 26, 27, 28 and 29, wherein one or more amino acid residues in said variant differs from the amino acid sequence of said penetrating peptide, provided that said variant differs in no more than 15% of amino acid residues from said amino acid sequence;
 - c) a fragment of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 24, 25, 26, 27, 28 and 29; and
 - d) a peptide comprising at least 12 contiguous amino acids of any of the peptides selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 24, 25, 26, 27, 28 and 29.
3. The penetrating peptide of claim 2, wherein the fragment is at least 10 amino acids in length.
4. The penetrating peptide of claim 2, wherein the amino acid sequence of said variant comprises a conservative amino acid substitution.
5. The penetrating peptide of claim 2, wherein the amino acid sequence of said variant comprises a non-conservative amino acid substitution.
6. The penetrating peptide of claim 1, wherein the amino acid sequence is SEQ ID NO: 3 or at least 12 contiguous amino acids thereof.
7. The penetrating peptide of claim 1, wherein the amino acid sequence is SEQ ID NO: 8 or at least 12 contiguous amino acids thereof.

8. The penetrating peptide of claim 1, wherein the amino acid sequence is SEQ ID NO: 9 or at least 12 contiguous amino acids thereof.
9. The penetrating peptide of claim 1, wherein the amino acid sequence is SEQ ID NO: 12 or at least 12 contiguous amino acids thereof.
10. The penetrating peptide of claim 1, wherein the amino acid sequence is SEQ ID NO: 24 or at least 12 contiguous amino acids thereof.
11. The penetrating peptide of claim 1, wherein the peptide is less than 30 amino acids long.
12. The penetrating peptide of claim 1, wherein the peptide is less than 25 amino acids long.
13. The penetrating peptide of claim 1, wherein the peptide is less than 20 amino acids long.
14. A penetrating peptide comprising at least one amino acid sequence selected from the group consisting of:
 - a) $(BX)_4Z(BX)_2ZXB$;
 - b) $ZBXB_2XBXB_2XBX_3BXB_2X_2B_2$;
 - c) $ZBZX_2B_4XB_3ZXB_4Z_2B_2$;
 - d) $ZB_9XBX_2B_2ZBXZBX_2$;
 - e) $BZB_8XB_9X_2ZXB$;
 - f) $B_2ZXZB_5XB_2XB_2X_2BZXB_2$;
 - g) $XB_9XBXB_6X_3B$;
 - h) $X_2B_3XB_4ZBXB_4XB_nXB$;
 - i) $XB_2XZBXZB_2ZBXB_3BZXBX_3B$;
 - j) $BZXBXXZ_2B_4XBX_2B_2XB_4X_2$;
 - k) $BZXBXXZ_2B_4XBX_2B_2XB_4$;

- l) $B_2XZ_2XB_4XBX_2B_5X_2B_2$;
- m) $B_qX_tZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
- n) $B_2ZX_3ZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
- o) $X_3ZB_6XBX_3BZB_2X_2B_2$; and
- p) at least 12 contiguous amino acids of any of peptides a) through o)

wherein

- q is 0 or 1;
- m is 1 or 2;
- n is 2 or 3;
- t is 1 or 2 or 3; and
- X is any amino acid;
- B is a hydrophobic amino acid; and
- Z is a charged amino acid;

wherein said penetrating peptide is capable of translocating across a biological barrier and wherein the penetrating peptide is coupled to an effector.

15. The penetrating peptide of claim 14, wherein said effector is a bioactive peptide.
16. The penetrating peptide of claim 15, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF), α MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.
17. The penetrating peptide of claim 14, wherein said effector is a pharmaceutically active agent.
18. The penetrating peptide of claim 17, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, and a therapeutic agent.

19. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 2.
20. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 6.
21. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 7.
22. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 8.
23. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 9.
24. A method of translocating a penetrating peptide across a biological barrier, wherein the penetrating peptide is the penetrating peptide of claim 10.
25. A penetrating peptide comprising at least one penetrating peptide having an amino acid sequence selected from the group consisting of:
 - a) $(BX)_4Z(BX)_2ZXB$;
 - b) $ZBXB_2XBXB_2XBX_3BXB_2X_2B_2$;
 - c) $ZBZX_2B_4XB_3ZXB_4Z_2B_2$;
 - d) $ZB_9XBX_2B_2ZBXZBX_2$;
 - e) $BZB_8XB_9X_2ZXB$;
 - f) $B_2ZXZB_5XB_2XB_2X_2BZXB_2$;
 - g) $XB_9XBXB_6X_3B$;
 - h) $X_2B_3XB_4ZBXB_4XB_nXB$;
 - i) $XB_2XZBXZB_2ZBX_3BZBX_3B$;
 - j) $BZXBXXZ_2B_4XBX_2B_2XB_4X_2$;
 - k) $BZXBXXZ_2B_4XBX_2B_2XB_4$;

- l) $B_2XZ_2XB_4XBX_2B_5X_2B_2$;
- m) $B_qX_tZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
- n) $B_2ZX_3ZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
- o) $X_3ZB_6XBX_3BZB_2X_2B_2$; and
- p) at least 12 contiguous amino acids of any of peptides a) through o)

wherein

- q is 0 or 1;
- m is 1 or 2;
- n is 2 or 3;
- t is 1 or 2 or 3; and
- X is any amino acid;
- B is a hydrophobic amino acid; and
- Z is a charged amino acid;

wherein said penetrating peptide is capable of translocating across a biological barrier and wherein said penetrating peptide is fused to an effector.

- 26. The penetrating peptide as in any one of claims 1, 14, and 25, wherein translocation across a biological barrier occurs within a tissue selected from the group consisting of: epithelial cells and endothelial cells.
- 27. The penetrating peptide as in any one of claims 1, 14 and 25, wherein said biological barrier is selected from the group consisting of: tight junctions and the plasma membrane.
- 28. The penetrating peptide of claim 25, wherein the effector is selected from the group consisting of: a bioactive peptide and a pharmaceutically active agent.
- 29. The penetrating peptide of claim 28, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor,

erythropoietin, GM-CSF, α MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, an LHRH analog, and neurotrophic factors.

30. The penetrating peptide of claim 28, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, a vitamin, an immunomodulator, an enzyme, an antineoplastic agent, heparin, methotrexate, and a therapeutic agent.
31. A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating peptide according to claim 25, and a pharmaceutically acceptable carrier.
32. The pharmaceutical composition of claim 31, wherein the composition further comprises a mixture of at least two substances selected from the group consisting of a non-ionic detergent, an ionic detergent, a protease inhibitor; and a reducing agent.
33. The pharmaceutical composition of claim 32, wherein the non-ionic detergent is a poloxamer.
34. The pharmaceutical composition of claim 33, wherein the poloxamer is pluronic F-68.
35. The pharmaceutical composition of claim 32, wherein the ionic detergent is a bile salt.
36. The pharmaceutical composition of claim 35, wherein the bile salt is Taurodeoxychilate.

37. The pharmaceutical composition of claim 32, wherein the protease inhibitor is selected from the group consisting of aprotonin and soya bean trypsin inhibitor.
38. The pharmaceutical composition of claim 32, wherein the reducing agent is NAC.
39. A method of producing a penetrating peptide comprising the penetrating peptide of claim 1 and an effector, said method comprising coupling said effector to said penetrating peptide.
40. The method of claim 39, wherein the coupling of said effector is achieved by a covalent bond.
41. The method of claim 40, wherein said covalent bond is a peptide bond.
42. The method of claim 40, wherein the covalent bond is achieved by a homo- or a hetero-functional bridging reagent.
43. The method of claim 42, wherein the bridging reagent is a succinimidyl-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC)-type reagent.
44. The method of claim 40, wherein the covalent bond is achieved by a peptide linker.
45. The method of claim 44, wherein the peptide linker has the sequence of SEQ ID NO: 16 or SEQ ID NO:17.
46. The method of claim 44, wherein the peptide linker can be cleaved by an enzyme.
47. The method of claim 46, wherein the peptide linker is designed to be cleaved by an enzyme conditionally activated under a certain physiological state and wherein the released effector favorably influences that physiological state.

48. The method of claim 39, wherein the coupling of said effector is achieved by a non-covalent bond.
49. The method of claim 48, wherein the non-covalent bond is achieved by an attachment of a hydrophobic moiety to the penetrating peptide, wherein the hydrophobic moiety enables penetrating module to be incorporated at the interface of a hydrophobic vesicle in which the effector is contained.
50. The method of claim 48, wherein the non-covalent bond is the result of a biotin-avidin or biotin-streptavidin interaction.
51. A method of translocating an effector across a biological barrier, said method comprising:
 - a) coupling said effector to the penetrating peptide of claim 1 to form a penetrating module; and
 - b) introducing said penetrating module to the biological barrier.
52. A method of oral vaccination, wherein the method comprises administering to subject the penetrating peptide of claim 1 coupled with a desirable antigen.
53. A kit comprising, in one or more containers, a therapeutically or prophylactically effective amount of the pharmaceutical composition of claim 31.
54. A method of treating or preventing a disease or pathological condition, said method comprising administering to a subject in which such treatment or prevention is desired, the pharmaceutical composition of claim 31, in an amount sufficient to treat or prevent said disease or said pathological condition in said subject.
55. The method of claim 54, wherein said disease or said pathological condition is selected from a group consisting of endocrine disorders, diabetes, infertility, hormone deficiencies, osteoporosis, neurodegenerative disorders, Alzheimer's

disease, Parkinson's disease, Huntington's disease, cardiovascular disorders, atherosclerosis, hypercoagulable states, hypocoagulable states, coronary disease, cerebrovascular events, metabolic disorders, obesity, vitamin deficiencies, haematological disorders, and neoplastic disease.

56. A method for producing the penetrating peptide of claim 25 comprising
- a) transfecting a production cell with a vector comprising a nucleic acid molecule of a fusion protein encoding said penetrating peptide and an effector operably linked to an expression control sequence;
 - b) culturing said production cell under conditions that permit production of a fusion protein consisting of the penetrating peptide and an effector peptide; and
 - c) isolating said fusion protein.
57. A peptide comprising an amino acid sequence, wherein said peptide is derived from a pathogenic bacteria, and said peptide is characterized by the ability to penetrate biological barriers *in vivo*.
58. The peptide of claim 57, wherein the peptide is derived from an integral membrane protein.
59. The peptide of claim 57, wherein the peptide is derived from a bacterial toxin.
60. A peptide comprising an amino acid sequence, wherein said peptide is derived from a nonpathogenic bacteria, and said peptide is characterized by the ability to penetrate biological barriers *in vivo*.
61. The peptide of claim 60, wherein said peptide is derived from an integral membrane protein.

62. The peptide of claim 60, wherein the peptide is derived from an extracellular protein.
63. A peptide comprising an amino acid sequence, wherein said peptide is derived from a human neurokinin receptor, and said peptide is characterized by the ability to penetrate biological barriers *in vivo*.
64. A penetrating module comprising at least one penetrating peptide having an amino acid sequence selected from the group consisting of:
- a) $(BX)_4Z(BX)_2ZXB$;
 - b) $ZBXB_2XBXB_2XBX_3BXB_2X_2B_2$;
 - c) $ZBZX_2B_4XB_3ZXB_4Z_2B_2$;
 - d) $ZB_9XBX_2B_2ZBXZBX_2$;
 - e) $BZB_8XB_9X_2ZXB$;
 - f) $B_2ZXZB_5XB_2XB_2X_2BZXB_2$;
 - g) $XB_9XBXB_6X_3B$;
 - h) $X_2B_3XB_4ZBXB_4XB_nXB$;
 - i) $XB_2XZBXZB_2ZB_3BZXB_3B$;
 - j) $BZXBXZX_2B_4XBX_2B_2XB_4X_2$;
 - k) $BZXBXZX_2B_4XBX_2B_2XB_4$;
 - l) $B_2XZ_2XB_4XBX_2B_5X_2B_2$;
 - m) $B_qX_tZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
 - n) $B_2ZX_3ZB_mX_qB_4XBX_nB_mZB_2X_2B_2$;
 - o) $X_3ZB_6XBX_3BZB_2X_2B_2$; and
 - p) at least 12 contiguous amino acids of any of the peptides a) through o)

wherein

- q is 0 or 1;
- m is 1 or 2;
- n is 2 or 3;
- t is 1 or 2 or 3; and
- X is any amino acid;

B is a hydrophobic amino acid; and
Z is a charged amino acid;

wherein said penetrating module is capable of translocating across a biological barrier and wherein said penetrating peptide is fused to molecular vessel, wherein said molecular vessel encloses an effector.

65. The penetrating module of claim 64, wherein the effector is selected from the group consisting of: a bioactive peptide and a pharmaceutically active agent.
66. The penetrating module of claim 65, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, GM-CSF, α MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, an LHRH analog, and neurotrophic factors.
67. The penetrating module of claim 65, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, a vitamin, an immunomodulator, an enzyme, an antineoplastic agent, heparin, methotrexate, and a therapeutic agent.
68. The penetrating module of claim 64, wherein the molecular vessel is selected from the group consisting of a soluble receptor, a minireceptor, and a binding protein.
69. The penetrating module of claim 68, wherein the soluble receptor is a soluble insulin receptor.
70. The penetrating module of claim 69, wherein the effector is insulin.
71. The penetrating module of claim 68, wherein the minireceptor is the ligand-binding domain of the insulin receptor.

72. The penetrating module of claim 71, wherein the effector is insulin.
73. The penetrating module of claim 68, wherein the binding protein is Intrinsic factor.
74. The penetrating module of claim 73, wherein the effector is vitamin B12.
75. A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating module according to claim 64, and a pharmaceutically acceptable carrier.
76. A method for producing the penetrating peptide of claim 25 comprising using solid-phase synthesis of the peptide.
77. The penetrating peptide of claim 15, further comprising a chemical modification.
78. The penetrating peptide of claim 77, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF), α MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.
79. The method of claim 56, wherein the fusion protein is further chemically modified.
80. The method of claim 79, wherein the chemical modification comprises the attachment of one or more polyethylene glycol residues to the fusion protein.